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Reducing pain by moving? A commentary on Ferrè et al. 2013

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Strong connections and mutual interactions between the vestibular and nociceptive systems are reflected in an early and widely use of devices for vestibular stimulation (e.g. hanging beds) to alleviate pain (Grabherr, Macauda, & Lenggenhager, 2015). Corroboratory, clinical evidence suggested artificial vestibular stimulation successful in temporarily relieving various symptoms of neuropathic pain (André, Martinet, Paysant, Beis, & Le Chapelain, 2001; McGeoch et al., 2009). Yet, only recently, a direct beneficial influence of *artificial* vestibular stimulation on pain was experimentally demonstrated in healthy participants (Ferrè, Bottini, Iannetti, & Haggard, 2013). These authors used a strong, unilateral vestibular stimulation induced by irrigating iced water into the left ear. This non-physiological stimulus activates the peripheral vestibular system and induces strong illusory self-motion and often vertigo (Lopez & Blanke, 2014) and, according to this recent study, reduces sensitivity to heat pain. Inspired by this highly relevant finding, we set out to test whether a similar analgesic effect could be induced by *natural* vestibular stimulation (i.e. by head/body motion on a chair) contrasting the previously used *artificial* vestibular stimulation. There are several important physiological differences between the different vestibular stimulation techniques (see Palla & Lenggenhager, 2014), and, in view of a potential therapeutic use, it is central to understand what aspects of the stimulation could contribute to its analgesic effects. Hence, we intended to extend and complement their findings by investigating the influence of *natural* vestibular stimulation on heat pain detection thresholds (see SOM for additional sensory detection thresholds neurophysiological measures). In order to test whether effects truly relate to the vestibular stimulation or to the sensation/illusion of moving in general, we included visual optokinetic stimulation (i.e. coherently moving dots to induce illusory self-motion in the opposite direction (vection; Brandt, Dichgans, & Koenig, 1973)). A visual stimuli with incoherently moving random dots that does not induce illusory self-motion was used as further control condition. Since a direct interaction between vestibular and nociceptive input has been suggested (Ferrè et al., 2013, Ferrè et al. 2015), we expected *natural* vestibular stimulation to increase heat pain thresholds. If the feeling of moving through space rather than the vestibular stimulation itself reduces pain (Lenggenhager & Lopez 2015), a similar effect could be expected for the optokinetic stimulations. No increase of pain thresholds was expected for the random dots condition.

Twenty healthy, right-handed men participated (mean age 31.1 ± 9.37, range 20 - 54) and provided written informed consent before participating in this study that had been approved by the local ethic committee and was conducted in accordance with the Declaration of Helsinki.
Participants underwent two experimental blocks in counter-balanced order, one assessing "*subjective"* threshold measures (comparable to the method used by (Ferrè et al., 2013), see below) and one assessing "*objective"* heat pain evoked potentials (see SOM)).

*** please insert somewhere here Figure 1 ***

In the "*subjective block"*, heat pain thresholds (HPT) were assessed at the dorsum of the left hand using the quantitative sensory testing (QST) method (temperature slope, 1°C/s; baseline temperature, 32°C (Maier et al., 2010)) with the TSA 2001-II device (MEDOC, Ramat Yishai, Israel). The left hand was chosen in all conditions, as right hemispheric dominance in right-handed participants has been shown for vestibular processes (Dieterich et al., 2003). As in Ferrè et al. (2013), a baseline measure was always taken first. The vestibular and the visual stimulation mini-blocks were counterbalanced and each included three conditions presented again in counterbalanced order (cp. Figure 1A).
For the vestibular stimulation, participants were seated in complete darkness upright and head restrained on a 3D-turntable (Acutronic, Switzerland). Three frequencies of sinusoidal yaw oscillation were used: 0.1, 0.3 and 0.7 Hz. The peak angular velocity, the relevant stimuli for the vestibular system, was 30 deg/s at all frequencies and, consequently, the chair sinusoidally oscillated between -47° to +47° at 0.1 Hz, between +/-16° at 0.3 Hz and between +/-7° at 0.7 Hz.
Full-field visual stimulation on a head mounted display (Oculus Rift, Oculus, Irvine, USA) was used. White dots were moving at a constant velocity either coherently to the left, coherently to the right or randomly to all directions.

The results of the stimulation related changes in HPT with respect to the baseline measure are depicted in Figure 1B. While one sample t-tests revealed that all stimulation conditions were different than baseline (all $p < 0.005$, Bonferroni corrected alpha = 0.008), a repeated measures one way ANOVA suggested no

difference between the effect of the six different stimulation conditions ($F(2.92, 55.51) = .88$, $p = .45$). As classical null hypothesis testing is not equipped to draw conclusions from non-significant results (e.g. Dienes, 2014), we additionally calculated a Bayes Factor (BF) for a repeated measures ANOVA model with factor condition (six levels) with the BayesFactor package (Rouder, Morey, Speckman, & Province, 2012) for the statistical programming language R (http://www.**r-project**.org/). The results confirmed the strong evidence in favor of the null model (no difference between stimulation) with a BF of 11.11 ($BF_{\text{Null Model}}/BF_{\text{condition}}$). The average increase over baseline in our study (mean 1.96°C) was exactly the same to the one found by Ferrè et al. (2013; 1.96°C).

In conclusion, our data suggest that while all vestibular and visual stimulations significantly increase heat pain thresholds as compared to baseline, they do not differ from each other. The fact that even the random dots stimulation, which should not activate the vestibular system, increases the pain threshold by about the same amount as actual vestibular stimulation, suggests however, to our opinion, rather non-specific effects causing the general decrease in heat pain sensitivity, plausibly linked to distraction (Bantick et al., 2002). Ferrè and co-authors (2013) excluded such non-specific effects as an interpretation of their data (a) as the thresholds were modulated in the opposite direction for pain and tactile detection thresholds (Ferrè et al., 2013), (b) as they remained stable after the CVS (Ferrè et al., 2013), while attentional effects should decrease and (c) as they found an early modulation of pain evoked potentials (Ferrè, Haggard, Bottini, & Iannetti, 2015). In their study the threshold was measured post-CVS, thus when there was no actual stimulation, nor any subjective (e.g. vertigo) or objective (nystagmus) signs of the vestibular stimulation. Nevertheless, Ferrè and colleagues (2013) argue that CVS is known to last for several minutes after the end of stimulation. The fact that we did not find any specific effect of stimulation could originate from the difference in the methods used, which are likely to activate slightly different cortical networks (Lopez, Blanke, & Mast, 2012 for a meta-analysis). Yet, due to movement constraints in the fMRI, the network involved in *natural* vestibular stimulation remains largely unknown. Furthermore, in view that ice-water is a very strong vestibular stimulus; one could argue that the vestibular stimulation used in our study was simply not strong enough. Against this hypothesis, however, speaks that the increase in threshold compared to baseline in our study was identical to Ferrè et al.

(2013). Further studies should clarify the intriguing possibility that real and illusory self-motion alleviates pain.

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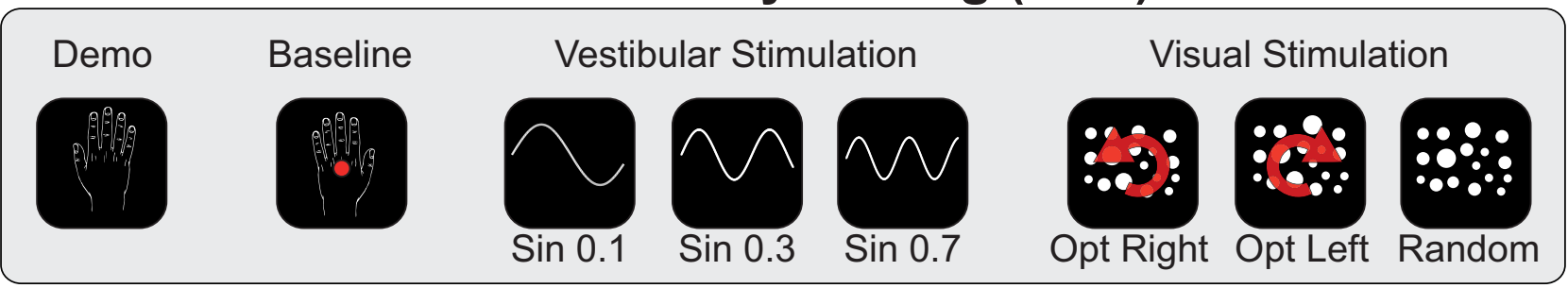
Figure Caption:

Figure 1. Experimental design and main result. A) Experimental Set-Up. Participants always underwent a baseline measurement for the quantitative sensory testing (QST) first. The order of the vestibular and visual stimulation mini-blocks was counterbalanced and the conditions within those mini-blocks were counterbalanced as well. The red arrow corresponds to the real or illusory motion direction, respectively. B) Changes in the heat pain thresholds (HPTs) compared baseline presented in box plots. While, all conditions lead to increased HPT compared to the baseline, a repeated measures ANOVA revealed no effect of condition (see text for more details).

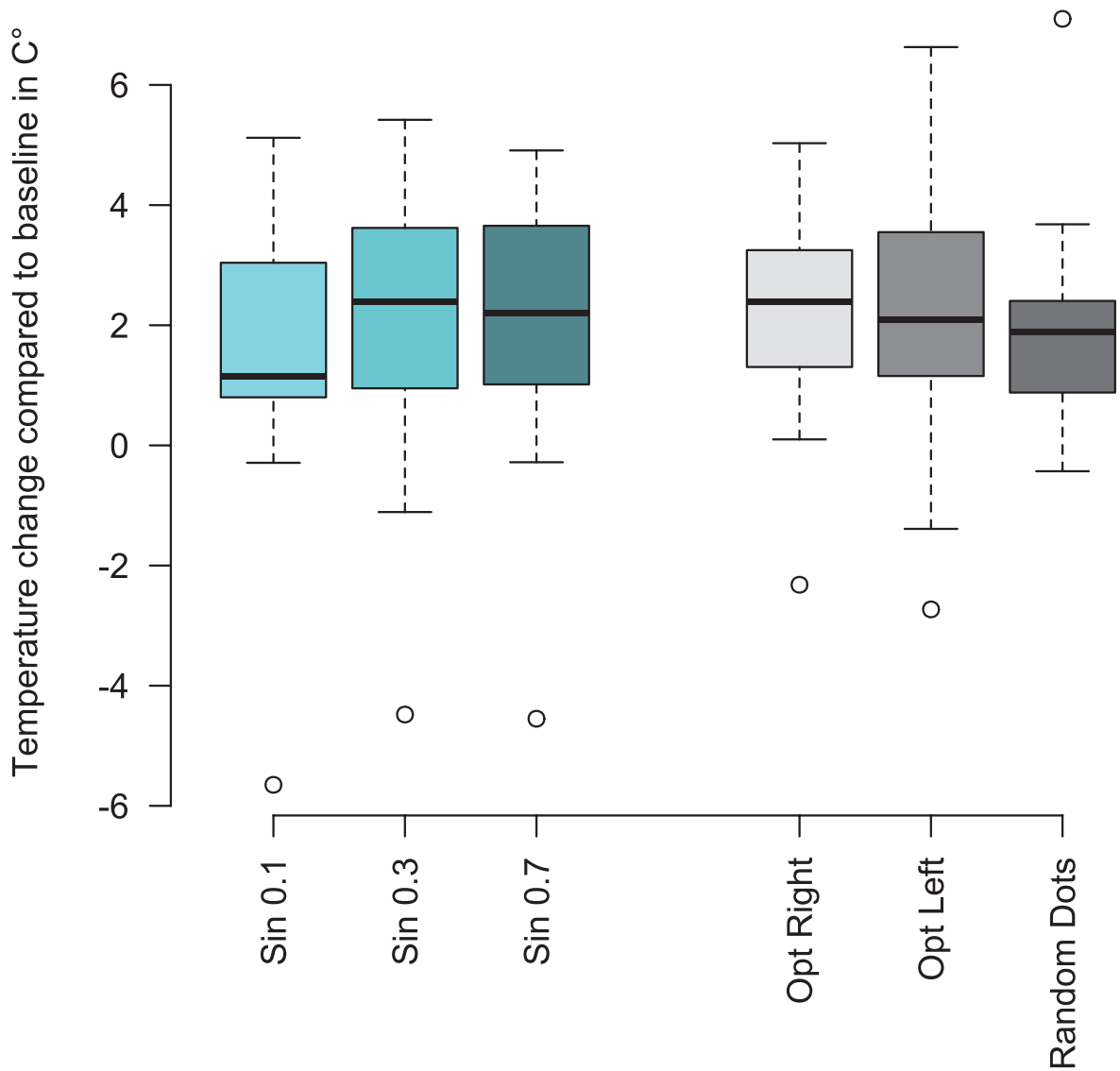
A

Quantitative Sensory Testing (QST) Block



B

Boxplot of HPT changes for each Condition



Supplementary Material to:

Reducing pain by moving? A commentary to Ferrè et al. (2013)

1. Supplementary methods

1.1 Participants

20 healthy, right-handed (according to the Edinburgh handedness inventory (Oldfield, 1971)) men participated. Only participants with normal Quantitative Sensory Testing (QST) parameters (Maier et al., 2010) at the baseline measurement were included in the sample. All participants gave written informed consent. The study protocol was approved by the local ethic committee and was in accordance with the principles of the Declaration of Helsinki 2008 and the guidelines of Good Clinical Practice (clinicaltrials.gov Identifier: NCT02358954).

1.2 General procedure

Participants underwent two experimental blocks (see Figure S1), which were presented in counterbalanced order.

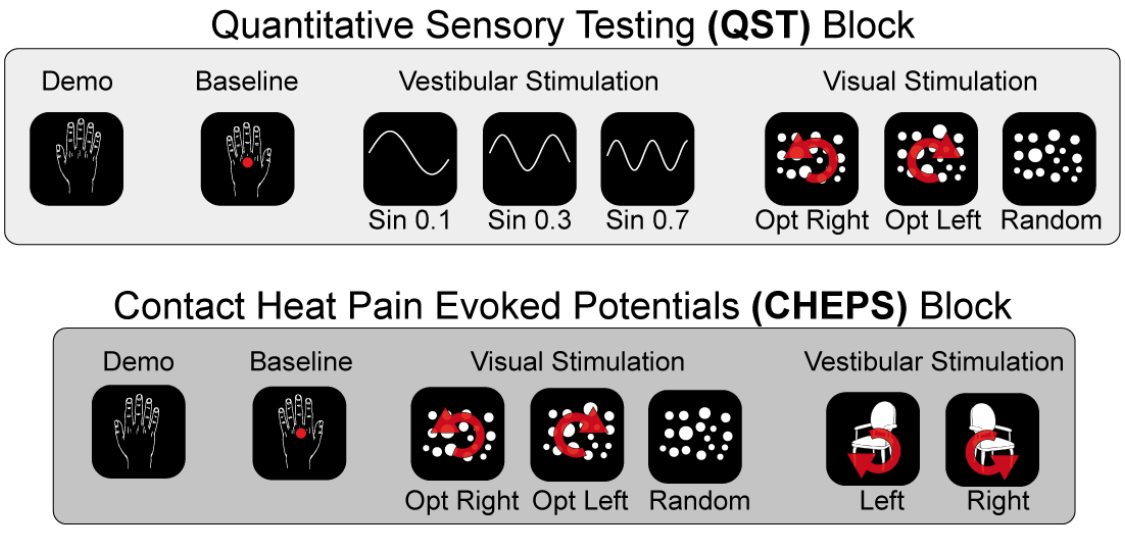


Figure S1: Complete experimental procedure. The two experimental blocks (QST block and CHEPS block) were presented in counterbalanced order. For each block, a demonstration (demo) was first performed on the right hand in order to familiarize the participant with the method, always followed by a baseline measurement on the left hand, followed the two experimental mini-blocks (visual and vestibular) which were presented in counterbalanced order. The conditions within the mini-blocks were counterbalanced as well. The red arrow corresponds to the (illusory) movement of the participants.

1.2.1. Quantitative Sensory Testing

In the *QST block* quantitative sensory testing was used on the dorsum of the left hand to assess the following subjective thresholds: Cold detection threshold (CDT), Warmth detection threshold (WDT), Cold pain threshold (CPT) and Heat pain thresholds (HPT). QST parameters were acquired according to the standardized protocol of the German Research Network on Neuropathic Pain (Maier et al., 2010; Rolke et al., 2006) using the methods of limits (temperature slope, 1°C/s; baseline temperature 32°C) with the TSA 2001-II device (MEDOC, Ramat Yishai, Israel).

1.2.2 Contact Heat Evoked Potentials

In the *CHEPS block* we assessed contact heat evoked potentials induced by a heat pulse stimulator (CHEPS, Medoc Ltd., Ramat Yishai, Israel) attached to the dorsum of the left hand. The thermode, with a contact activation area of 573 mm^2, uses a combination of a heating foil and a Peltier element to generate the fast heating and cooling rate. We used the maximum rates available (a heating rate of 70 °C/s and a return rate of 40 °C/s). The stimulus duration was approximately 800ms (271ms from baseline to peak temperature and 475ms to return to baseline (Roberts et al., 2008)). CHEPs were sampled at 2 kHz using a single channel preamplifier (bandpass filter 0.25-300 Hz, ALEA Solutions, Zurich, Switzerland). The heat pulses were applied from a baseline temperature of 32 °C to a peak temperature of 52°C with an inter-stimulus interval that varied randomly between 8 and 12 s (end-to-onset interval) on the dorsum of the left hand (Kramer, Haefeli, & Jutzeler, 2012).

1.3 Vestibular stimulation

Subjects were seated upright on a 3D-turntable with three servo-controlled motor-driven axes (conceived by Prof. V. Henn, designed and manufactured prototype built by Acutronic, Switzerland). Only rotations around the earth vertical (yaw) axis were used in the current experiment. The head was restrained with an individually moulded thermoplastic mask (Sinmed BV, Reeuwijk, Netherlands). Subjects were positioned so that the intersection of the inter-aural and naso-occipital axes was at the intersection of the three axes of the turntable. Pillows and safety belts minimized movements of the body.

1.3.1 Vestibular stimulation during QST

In order to assess the effects of vestibular stimuli on pain thresholds, a sustained constant natural vestibular activation over the time of the QST was necessary. As perceptual responses to sustained angular motion stimuli decay over time (Bertolini et al., 2011; Okada, Grunfeld, Shallo-Hoffmann, & Bronstein, 1999), we decided to use an oscillatory motion profile of the chair with three frequencies: 0.1, 0.3 and 0.7 Hz, defined as Sin 0.1, Sin 0.3 and Sin 0.7. The peak velocity (the relevant stimulus for the vestibular system) was 30 deg/s at all frequencies. Testing of sinusoidal stimuli at different frequencies was necessary to obtain a sustained cover of the spectrum of natural angular stimulation of the vestibular response (Fernandez & Goldberg, 1971; Leigh & Zee, 2006) and, concurrently, provided a frequency response characterization in line with previous vestibular studies (Bockisch, Straumann, & Haslwanter, 2005).

1.3.2 Vestibular stimulation during CHEPS

As evoked potential in CHEPS occurs over a time span < 1 s, we used a natural vestibular stimulus consisting of a 120 deg impulsive rotation with a maximal rotation of 450 deg/s. The chair movement was synchronized with the evoked potentials and the thermic stimulus arrived 300 ms after initiating the movement. The difference between the stimuli used for the threshold measurements (sinusoidal stimuli) and those for evoked potential measurement (impulsive stimuli) allowed matching the time scale of the vestibular stimulation to that of each measurement. We defined chair left as the passive counter clockwise and chair right as the passive clockwise rotation.

1.4 Visual Stimulation

Full-field visual stimulation consisting of white dots of different sizes moving on a black background at 30 deg/s was used. A head mounted display (Oculus Rift, Oculus, Irvine, USA) provided the visual stimuli created in ExpyVR (http://lnco.epfl.ch/expyvr). In the "optokinetic stimulation left" and the "optokinetic stimulation right" conditions the dots were coherently moving to the right or left respectively, inducing illusory self-motion (vection; Brandt et al., 1973) to the left or right, respectively. In the "random dots condition" the dots were moving incoherently in random directions, inducing therefore an overall null visual motion and no self-motion illusion.

1.5 Measurements

1.5.1 Subjective thresholds in the QST block

Participants had to press a button as soon as they felt the slightest change of temperature to "cold" or "warm" (cold detection threshold (CDT) or warmth detection threshold (WDT), respectively). For the cold pain threshold (CPT) and heat pain threshold (HPT) participants had to press the stop button immediately at the first painful sensation. Each measure was repeated 3 times for each condition and a mean threshold temperature was calculated. All thresholds were obtained with ramped stimuli (1 °C/s) that were terminated when the subject pressed a button. For thermal detection thresholds the ramp back to baseline was 1 °C/s, while for thermal pain thresholds this ramp was chosen at maximum device capacity resulting in nominal ~5 °C/s (Rolke et al., 2006).

1.5.2 Pain intensity ratings during the CHEPS block

The perceived pain intensity was assessed after each of the 10 stimulations per condition according to a 0 to 10 numerical rating scale (NRS). An auditory cue 2 seconds after stimulation indicated the participants to verbally tell the experimenter the intensity rating (Kramer et al., 2012).

1.5.3 Cortical pain evoked potentials during the CHEPS block

Cortical recording electrodes were positioned according to the International 10-20 system based on available guidelines (Cruccu et al., 2008). N2/P2 was acquired from an active vertex-recording electrode (Cz) referenced to the nose. A contralateral temporal active recording electrode (T4) referenced to Fz was used to acquire N1/P1 potentials.

1.5.4 Motion sickness during both blocks

The sensitivity to motion sickness differs strongly between individuals (Golding & Gresty, 2015; Lackner, 2014). To quantify the possible influence of motion sickness on our results, we monitored its level after each stimulation trial using a simplified Pensacola scale from 0 to 20 (Dai, Kunin, Raphan, & Cohen, 2003).

1.5.4 Self-motion during all visual stimulations

A Visual Analog Scale (VAS) scale (0= no self-motion, 10 = strong self-motion) after the two optokinetic stimulations and the presentation of the random dots was used in order to assess intensity of induced illusory self motion.

1.6 Statistical Analysis

Statistical analysis was performed using the statistical programming language R version 3.0.2 (http://www.**r-project**.org/) including the BayesFactor package (Rouder, Morey, Speckman, & Province, 2012) and WRS2 package (WRS2: Wilcox robust estimation and testing; Mair, Schoenbrodt, & Wilcox, 2015).

1.6.1 QST data

The raw QST data was transformed to temperature changes by subtracting the baseline values from each condition. We first run Bonferroni-corrected ($p = .008$) one-sample t-test for each difference to test whether they were significantly different from zero, i.e. baseline. We then used a one-way ANOVA for all conditions Sin 0.1, Sin 0.3, Sin 0.7, Optokinetic Stimulation Right, Optokinetic Stimulation Left, Random dots).

1.6.2 CHEPS data

Pain intensity rating

As baseline N1 potentials were missing, we excluded six participants from all CHEPS data analyses (new $n = 14$). The raw NRS data was transformed to pain perception changes by subtracting the baseline values from each condition. We first ran Bonferroni corrected ($p = .01$) one sample t-test for each difference to test whether they were significantly different from zero, i.e. baseline. Afterwards a repeated measures one way ANOVA was calculated with the following conditions: Vestibular Stimulation left, Vestibular Stimulation right, Optokinetic Stimulation Right, Optokinetic Stimulation Left, Random dots.

Pain evoked potential data

Potentials were manually detected and where considered not present if we could not detect a peak wave in relation to the background small unreliable CHEPs (<10μV) were discarded (Haefeli, Kramer, Blum, & Curt, 2013). In case no potential was

detected the amplitude was coded as 0 (see Untergehrer, Jordan, Eyl, & Schneider, 2013 for a comparable approach). We first ran Bonferroni corrected (p=0.01) one sample t-test for each difference to test whether they were significantly different from zero, i.e. baseline. Afterwards a repeated measures one way ANOVA was calculated with conditions (Vestibular Stimulation left, Vestibular Stimulation right, Optokinetic Stimulation Right, Optokinetic Stimulation Left, Random dots) for the amplitudes of N1, N2 and P2.

2. Supplementary results

The descriptive results are shown in Table S1 and S2.

	Baseline	Sin01	Sin03	Sin07	Vest. stim left	Vest. stim right	Opt. kin. left	Opt. kin. right	Random Dots
HPT	45.29 (± 2.60)	46.86 (± 3.49)	47.24 (± 2.81)	47.28 (±2.93)			47.44 (± 2.17)	47.49 (± 2.45)	47.13 (± 2.33)
CPT	16.56 (± 9.73)	15.54 (± 9.74)	14.27 (± 9.42)	13.97 (± 10.06)			14.49 (± 10.00)	14.77 (± 10.76)	14.31 (± 10.15)
WDT	34.09 (± 0.87)	38.18 (± 2.87)	38.39 (± 2.79)	38.53 (± 2.50)			39.20 (± 2.60)	39.23 (± 3.06)	38.68 (± 2.82)
CDT	30.69 (± 0.67)	29.02 (± 2.43)	28.23 (± 3.99)	29.84 (± 3.56)			28.67 (± 2.81)	28.46 (± 2.64)	28.82 (± 2.23)
NRS-Pain	1.94 (± 1.00)				1.71 (± 1.07)	1.51 (± 1.05)	1.19 (± 0.78)	1.49 (± 0.85)	1.84 (± 1.25)
N1 A	-8.02 (± 3.50)				-11.73 (± 9.26)	-6.40 (± 6.01)	-3.63 (± 3.18)	-4.06 (± 3.55)	-5.61 (± 4.80)
N2 A	-9.40 (± 3.97)				-8.04 (± 5.34)	-8.48 (± 6.14)	-5.09 (± 4.04)	-5.58 (± 3.87)	-5.97 (± 4.68)
P2A	9.41 (± 4.46)				8.15 (± 5.10)	6.62 (± 4.18)	3.72 (± 2.83)	5.72 (± 4.33)	5.22 (± 4.99)

Table S1. Means (± standard deviations). HPT, CPT, WDT and CDT are shown in °C.

	Sin01	Sin03	Sin07	Opt. kin. Left QST	Opt. kin. Right QST	Random Dots QST	Vest. stim left	Vest. stim right	Opt. kin. Left CHEPS	Opt. kin. Right CHEPS	Random Dots CHEPS
Motion-Sensation				4 (+- 2.71)	4.45 (+- 2.63)	1.5 (+- 1.67)			4 (+- 3.04)	4.29 (+- 2.97)	0.71 (+- 1.44)
Pensacola	0.65 (+- 1.14)	0.60 (+- 0.99)	0.65 (+-1.14)	1.10 (+- 1.45)	2.05 (+- 2.80)	0.65 (+- 2.06)	0.35 (+- 0.74)	0.92 (+- 1.44)	1.21 (+- 2.26)	1.36 (+- 2.21)	0.14 (+- 0.53)

Table S2. Means (± standard deviations)

2.1 QST

2.1.1 Cold pain thresholds

The one sampled t tests revealed that there were no differences significantly different from zero (all $p > .11$). The repeated measures ANOVA showed no effect of condition ($F(3.10, 58.94) = 1.54$, $p = .21$).

2.1.2 Warmth detection thresholds

The one sampled t tests revealed that all differences were significantly different from zero (all $p < .001$). The one-way ANOVA showed no effect of condition ($F(5,95) = 1.14$, $p = .0.35$).

2.1.3 Cold detection thresholds

Wilcoxon signed rank tests revealed that all differences were significantly different from zero (all $p < .003$).

2.2 NRS data

One sample t-tests revealed a difference significantly different from zero for the condition Optokinetic Stimulation right ($p < 0.001$). All other conditions t-tests showed no significant difference from zero (all $p > .022$). For the ANOVA, Mauchly's test indicated that the assumption of sphericity had been violated, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity ($e = .74$). The results show that the difference in pain perception was not significantly affected by the condition, $F(2.92, 38.48) =.1.68$, $p = 0.18$. The Bayesian ANOVA revealed a Bayes Factor of 0.44, i.e. slightly more evidence for the null hypothesis, yet more data would be needed for conclusive results.

2.3 Pain evoked potential data

2.3.1 N1 Amplitude

T-tests revealed a significant difference (i.e. a smaller amplitude) from zero for the condition Optokinetic Stimulation right and Optokinetic Stimulation left (all p-values < 0.01). All other conditions t-tests showed no significant difference from zero (all $p > .04$). For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $p < .001$, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity ($e = .37$). The results show that the difference in the N1 amplitude was significantly affected by the condition, $F(1.48, 19.24) = 8.17$, $p = .005$.

2.3.2 N2 Amplitude

T-tests revealed a significant difference (i.e. a smaller amplitude) from zero for the condition Optokinetic Stimulation left ($p < .01$). All other conditions t-tests showed no significant difference from zero (all $p > .03$). For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $p < .001$, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity ($e = .56$). The results show that the difference in the N2 Amplitude was not significantly affected by the condition, $F(2.24, 29.12) = 1.92$, $p = .16$.

2.3.3 P2 Amplitude

T-tests revealed a significant difference (i.e. a smaller amplitude) from zero for the condition Optokinetic Stimulation left and right ($p <.01$). In all other conditions t-tests showed no significant difference from zero (all $p > .01$). For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $p < .001$, therefore degrees of freedom were corrected using Huynh–Feldt estimates of sphericity ($e = .56$). The results show that the difference in the P2 amptliude was significantly affected by the condition, $F(2.32, 30.16) = 1.92$, $p = .03$.

2.4 Additional analyses

2.4.1 Motion sickness

For the motion sickness data a Friedman test revealed a significant effect of condition in the QST block ($X^2(5)=12.43$, $p = 0.03$) and in the CHEPS block ($X^2(4)=10.74$, $p = 0.03$).

2.4.2 Motion rating during visual stimulation

Optokinetic stimulation of coherently moving white dots to the left and right did induce a slight egomotion sensation (vection) during the QST ($X^2(2)=19.97$, $p < .001$) and the CHEPS block ($X^2(2)=20.91$, $p < .001$). Wilcoxon tests were used to follow up this finding. A Bonferroni correction was applied and so all effects are reported at a .016 level of significance. This analyses revealed higher motion sensations during both Optokinetic Stimulation right ($W=316.5$, $p=0.001$) and Optokinetic Stimulation left ($W=332$, $p<0.001$) in the QST as well in the CHEPS block (Optokinetic Stimulation right: $W=171$, $p<0.001$ and Optokinetic Stimulation left: $W=167$, $p=0.001$) as compared to the Random dots condition. The two Optokinetic

Stimulation conditions did not differ significantly neither in the QST (W=177.5, p=0.54) nor in the CHEPS block (W=91, p=0.76)

3. Supplementary discussion

Next to the main finding, reported in the manuscript our supplementary results suggest the following additional findings.

First, while the heat pain threshold was increased compared to baseline in all conditions (see main text), the cold pain threshold was not altered by any of our experimental manipulations. This findings could potentially be linked to differential physiological mechanisms underlying cold and warmth perception (e.g. Schepers & Ringkamp, 2010), or, alternatively, to the very large population standard deviation (mean 13.69°C; standard deviation 9.54) of the cold pain threshold (Maier et al., 2010), which might make the identification of a variation between conditions more difficult. *Second,* our data show that vestibular and optokinetic stimulation, as well as incoherently moving random dots influence thermal detection thresholds (warmth and cold detection) similar to pain detection thresholds, by generally decreasing sensitivity, i.e. warmth detection threshold was increased and cold detection threshold decreased during all stimulations as compared to baseline. *Third*, we could not show a decrease in the subjective evaluation of the pain during our CHEPs measurements Ferré and co-authors (2013) did in three subjects (experiment 2 of their study). This might be related to methodological differences, but could also question a general pain reduction induced by the vestibular stimulation (see also discussion in the main text). *Forth,* the electrophysiological data on the pain evoked potentials showed generally and contradictory to (Ferrè, Haggard, Bottini, & Iannetti, 2015), no influence of the vestibular stimulation on neither N1, N2 or P2. Amplitudes of N1 and P2 were both significantly reduced compared to baseline in both the optokinetic stimulation left and right condition, while N2 was reduced specifically in the optokinetic stimulation left condition. These data were however not corroborated by the subjective measure as by the pain ratings (see above), which did not differ from zero in any of the conditions. The electrophysiological results have to be considered with caution, as only 14 participants could be included due to missing clear typical pain-evoked components in the others. Moreover, with the current setup it is not possible to exclude that the effect could be linked to eye-movements. Both vestibular and visual motion stimuli induce reflexive eye movements, which, even if we carefully checked that participants

always fixated a red dot, evoke neural activity required to suppress the reflex. The current setup did not allow correcting for eye movements or eye movement suppression, which might have been strongest in the two optokinetic stimulation conditions. Alternatively, and more interestingly, the effect could be linked to motion sickness. Motion sickness is known to affect performances and reaction time already in case of sopite syndrome, i.e. conditions occurring at the onset of motion sickness or in presence of very mild nauseogenic stimuli, in which the symptoms are so low that the participants are often not able to recognize or report them (Lackner, 2014). In our experiment motion sickness was overall very low, but the highest values were found in both left and right optokinetic stimulation conditions, and is plausibly high as well during caloric vestibular stimulation (Ferrè et al., 2013; Ferrè et al., 2015), and could thus have mediated implicit nociceptive processes.

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